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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,528	02/23/2004	Arthur M. Brown	CWR-019285US CON	1521

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
01/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,528	BROWN ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,7,8,15 and 26-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,7,8,15 and 26-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 10, 2009 that includes a response to the advisory action dated November 18, 2009, has been entered. No claims were amended or cancelled. Claims 28-39 have been newly added. Accordingly, claims 4, 7, 8, 15 and 26-39 are pending in the application and under current examination.

Response, Maintained & New Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 4, 6-8, 15, 26 and 27 stand rejected and claims 28-39 are newly rejected under 35 U.S.C.§112, first paragraph, because the specification fails to provide an enablement for the full scope of the claimed invention. The rejection set forth on pp. 6-11 of the previous Office action dated March 27, 2007, pp. 3-7 of the Office action dated December 10, 2007, the advisory action dated May 6, 2008, pp. 2-4 of the Office action dated March 17, 2008, and the advisory action dated November 18, 2009 is maintained for claims 4, 7, 8, 15, 26 and 27 and further applied to new claims 28-39, for reasons of record.

As previously indicated, the specification is considered enabling for a method of inducing apoptosis in cultured cancer cell lines, comprising the step of introducing into said cells an expression vector comprising a nucleic acid encoding a human KChAP protein as set forth in SEQ ID NO: 2, said nucleic acid operably linked to a promoter active in cancer cell lines.

The previous Office actions indicated that the claims, when given their broadest reasonable interpretation in view of the as-filed specification, are directed to a method of inducing apoptosis in human prostate cancer cells or breast cancer cells in a tumor in a subject,

following delivery of a viral vector expressing the human KChAP protein, by intratumoral injection. Therefore the claims broadly embrace a method of tumor cancer therapy.

The prior art teachings of Kerbel et al., Vieweg et al. and Hoffman et al. were cited to demonstrate that orthotopically transplanted tumors do not necessarily recapitulate the 'encouraging' responses of their ectopically (usually subcutaneous) grown counterparts, and that the animal model exemplified in the instant specification, i.e. subcutaneously-growing human cancer cell lines in immunodeficient mice, do not sufficiently represent clinical cancer, especially with regard to metastasis and drug sensitivity. Moreover, a cancer cell line is not comprised of a mixture of cancer cells and normal cells, and in view of the additional issues previously highlighted, such delivery would likely also produce deleterious undesired consequences with respect to the promotion of unwanted cell proliferation.

As previously indicated, the heterotopic subcutaneous xenotransplantation of cell lines in an immunodeficient mouse fails to reflect human carcinoma. Additional issues relate to the use of cell lines (as opposed to primary tumor cells) and ectopic and heterotopic transplantation of said cell lines (versus orthotopic transplantation or primary tumor cells) in immunodeficient nude mice, constituting deficient cancer models, as well as the paradox that enhancement of K^+ channel activity can facilitate not only tumor cell apoptosis but also tumor cell proliferation, especially in a tumor mass comprising a mixed cell population, bringing into question the validity of the claimed method as a therapeutic, and specific teaching away from Applicants' claimed invention by the prior art of Wang (Eur. J. Physiol. 448:274-286; 2004), that states: "K^+ channels favor tumor cell proliferation, therefore, inhibition of K^+ channel function or down-regulation of K^+ channel expression should inhibit tumorigenesis…On the other hand, K^+ channels also promote apoptotic cell death…enhancement of K^+ channel activity can facilitate not only tumor cell apoptosis but also tumor cell proliferation. This apparent paradox confounds the manipulation of K^+ channel function and/or expression as an option for the treatment of cancers." (pp. 281-282 bridging).

Applicants disagree, and with reference to various case law and the Wands factors, argue that the specification is sufficient to enable the skilled artisan to make and use the method recited

in the claims using only routine experimentation.Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that a claim that is broad enough to cover multiple embodiments must enable all those embodiments. The Wands factors cited by Applicants are considered in determining whether a specification is enabling for the claimed invention, without undue experimentation on the part of the skilled artisan. The factors include the presence or absence of working examples, the nature of the invention, the state of the prior art and the predictablility or unpredictablility of the art.

The prior art with regard to potassium channels as potential therapeutic targets, at the time of the invention by Applicants is reviewed by Shieh et al. (Pharmacol. Rev. 52:557-593; 2000). The authors describe KChAP as a chaperone protein, or auxullary factor, regulating the function and expression of some of the Kv channels, such as Kv2.1, Kv1.3 and Kv4.3, and state that given the diversity of K^+ channel subunits, understanding the composition of channel complexes in vivo remains a challenge (first column, p. 566). Shieh et al. additionally state that K^+ channel activities play important roles in signal transduction pathways leading to proliferation, differentiation and cell fusion (second column, p. 574), that enhancement of current is directly involved in apoptosis and oncogenesis (first column, p. 575), and that overexpression of rEAG K^+ channels in Chinese hamster ovary or NIH 3T3 cells induces significant features characteristic of malignant transformation (second column, p. 575). The authors concluding that key hurdles in targeting K^+ channels remain to be resolved (second column, p. 577).

Thus, the prior art of Shieh et al. highlights the unpredictability with regard to targeting K^+ channel expression, and together with the post-filing art of Wang et al. argue against the overexpression of K^+ channels, as such is known to promoter malignancy.

The working examples cited by Applicants are not commensurate in scope with the claimed invention and are directed to using cell lines, that in turn fail to reflect the issues raised for normal breast and prostate tumors, comprising a mixture of normal and transformed cells. As also indicated in MPEP 2164.03, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). The working examples embody a number of deficiencies that do not allow one of skill in the art to

extrapolate their teachings to applications wherein a cancerous tumor may be treated in a subject. The evidence of record as a whole indicates that the heterotopic subcutaneous xenotransplantation of cell lines in an immunodeficient nude mouse fails to reflect human carcinoma, and therefore a person of skill in the art would need to carry out further experimentation, with an uncertain outcome and constituting undue experimentation to introduce a viral expression vector encoding KChAP, to be effective in inducing apoptosis and or treating a subject with prostate or breast cancer *in vivo*.

Therefore, it is not clear what Applicants' invitation to one skilled in the art to engage in some experimentation is supposed to encompass, as the unpredictability in targeting K^+ channels, and the teaching away from their overexpression has been made of record by factual evidence, Applicants' allegations to the contrary notwithstanding.

Applicants' arguments regarding the cancer models reviewed by Krebel and Vieweg are not found persuasive, because the references clearly set forth the unpredictability inherent to heterotopic cancer models.

Applicants' argument that Wang would not lead a skilled artisan to believe that further experimentation is needed to resolve the apparent paradox suggested by Wang when treating cancers, by stating: "over-expression of K^+ channels by infection of tumour cells with virus vectors carrying K+ channel cDNAs, will be feasible sooner or later", is not found persuasive, because the statement makes it clear that such treatment is not yet feasable and that obstacles in such approach need to be overcome. An invitation for further experimentation in a post-filing art is not indicative of an enabled disclosure in an application filed years earlier. Thus, a person of skill in the art would need to engage in further experimentation to resolve the paradox outlined by Wang, whose outcome is unpredictable and thus constitutes further undue experimentation, especially since a tumor mass contains a heterogeneous population of cells at different stages of cancer progression.

Applicants state that they fail to see the relevance of this argument because the claimed method is not directed to treating cancers. Applicants acknowledge that the present application contemplates treating a variety of cancers by induction of apoptosis. As claims are not interpreted in a vacuum, the disclosure must enable the skilled artisan to use the claimed method in a tumor of a human subject. However, a skilled artisan would not practice the claimed

invention in view of the evidence of record regarding the unpredictability and the deleterious consequences of over-expression of K^+ channels by delivery of vectors carrying K^+ channel cDNAs to tumour cells.

Applicants' reference to *In re Brana*, that in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development, ignores the critical Wands factor of predictability, that must be considered in an enablement rejection. Further experimentation is permissible when it is merely routine and predictable, however, in the instant case, enhancement of K^+ channel activity can facilitate not only tumor cell apoptosis but also tumor cell proliferation, and as indicated by Wang, this apparent paradox confounds the manipulation of K^+ channel function and/or expression as an option for the treatment of cancers.

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005); "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." The claimed methods of delivery and over-expression of KChAP protein constitute such a "germ of an idea". Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Therefore the rejection is maintained for claims 4, 7, 8, 15, 26 and 27, and further applied to new claims 26-39 for reasons of record and the foregoing response.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633